Late comments and responses relating to the first draft- and comments to the second draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds

Minor grammatical or spelling changes have been made without acknowledgment. Only substantial comments are listed.

Submissions and comments to the first draft are from Japan. Comments on first and second drafts from United States are merged in the table.

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
Japan	3	2	It is better to describe in detail the unintentional production process as well as paragraph 12, 23 and 97.	Some text has been edited. It is not relevant to describe in detail the process of unintentional production of PFHxS during ECF in the risk profile stage.
Japan	4	11	There is a lack of reference information as the basis for deriving such a theory. Especially, it is not clear about the mechanism involved in decomposition of PFHxS salts and other PFHxS related compounds and the range of substrates to be decomposed.	A reference has been added to "2.2.1 Persistence" in the document.
Japan	4	11	PFHxS salt should be described precisely separated from PFHxS related compounds because PFHxS salt does not degraded into PFHxS.	PFHxS salts are considered PFHxS-related compounds in this document. A non-exhaustive list of compounds can be found in Annex 1 of the POPRC14/INF document
Japan	6	Table 2	To be described as PFHxS-K micelle precisely.	The water solubility is reflected as described in Campbell et al 2009. Whether it is described as a micelle is not relevant. PFAS will direct itself a certain way in a water solution due to its hydrophilic- and hydrophobic properties.
Japan	6	Table 2	LogKow: To be described whether it is in dissociated state or in non-dissociated state.	Table has been edited
Japan	6	Table 2	LogKoa: To be described whether it is in dissociated state or in non-dissociated state.	Table has been edited
Japan	6	Table 2	LogKoc: To be described whether it is in dissociated state or in non-dissociated state.	Text has been edited. See * under table 2
Japan	6	18	It seems to include no-pure reviewed article in the reference list such as review articles and the data reports.	All published papers are peer-reviewed. Reports are in English and publicly available.

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
Japan	11	37	In this paragraph, there is no reference information as the basis for explanation. The references should be added.	Text has been edited based on comments from other Parties or Observers. References are added.
Japan	12	42	Sufficient data of similarity are not shown to apply read-across appoach. We would Japan like to delete this sentence because we understand at POPRC13 read-across approach will not be used for Risk Profile.	To our knowledge, it was not decided to exclude the read-across approach from the RP of PFHxS. Furthermore, some parties have requested that we use the read-across approach and make this clear in the draft RP.
Japan	12	43	We should discuss by concrete data which prove PFHxS precursors are degraded into PFHxS without anticipation nor theoretical assessment.	There is no reason to believe that PFHxS-precursors will not act in a similar way as PFOS- and PFBS-precursors in terms of degradation. To support your argument on the lack of degradation of PFHxS-related compounds, please provide peer-reviewed studies that confirm that PFHxS-precursors are not at any degree degraded to PFHxS.
Japan	12	44	POPRC members have discussed in the tone that FHxSA should be regulated because it has the potential to degrade to PFHxS. It is doubtful, however, to regulate FHxSA in the same group with PFHxS in spite of the situation where the concentration of FhxSA is lower than the concerend level.	FHxSA (perfluorosulfonamides) have the potential to break down to PFHxS in the environment and in organisms, therefore all substances that can degrade to PFHxS are included in the nomination.
Japan	12	45	Only facts should be described. This sentence is to be deleted if it is consideration by the auther of the risk profile.	This reflects what has been published in Codling et al 2014
Japan	13	47	I suppose the concentration in water for BCF calculation includes not only single compound but also micelle. It is doubtful whether micelles can be absorbed through cell wall. I propose to evaluate the test result under CMC.	The document states that BCF/BAF are under the criteria (5000). There is no need to evaluate further in this case. BAF/BCF is not used as an argument for bioaccumulation it is well known that PFASs accumulate in organisms through the binding to proteins.
Japan	14	51	"It was later discussed whether ruminants have the possibility to biodegrade PFHxS and other PFAS by ruminal microoganisms in the rumen of ruminants such as cows but this study was inconclusive (Kowalczyk et al., 2015).": This sentence should be deleted because only facts based on data should be described not contents of discussion.	The text reflects what has been published in the paper referenced.
Japan	14	54	"Processes that transport PFHxS, its salt and PFHxS related compounds to the Arctic include direct transport of compounds in air or water and/or indirect transport of neutral volatile precursor compounds that can undergo degradation	We are not sure which paper you are referring to but Butt et al 2010 states that "Volatile precursors via the atmosphere, degradation by atmospheric oxidation to PFCAs and

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			by atmospheric oxidation or by biological degradation (Butt et al., 2010; Ahrens et al., 2011; Alava et al., 2015, Wang et al., 2015)".: Although this paper described that PFHxS precursors could be degraded by biological degradation, the compounds can not be degraded in the atomospher or open water since these kind of compounds degraded under the anaerobic condition as described in the references. .	PFSAs and subsequent wet and dry deposition." To support your argument on the lack of degradation of PFHxS-related compounds in the air, please provide peer-reviewed studies that confirm that PFHxS-precursors are not at any degree degraded to PFHxS in the air. Furthermore, a number of studies show evidence that PFBS/PFOS-precursors are transported through air and degrade to e.g. PFBS, PFOS and most likely this also applies to PFHxS. This argument is strengthened by the detection of increasing amounts of PFHxS during snow melt and detection of PFHxS in rain water. See section 2.2.4
Japan	18	76	I suppose thyroid hormone is correctt becausse study on the African clawed frog (*Xenopus laevis*) tadpoles is executed for evaluation of thyroid-hormone action.	No, in this study they investigated growth and sexual development of amphibians, and used the brain as a full-fledged sexual organ as a substitute for gonads.
Japan	19	80	The draft sentence describes only the single dose (10mg/kg). The range of dose should be shown for dose-dependency.	Text has been edited.
Japan	19	85	Paragraph 85 should be deleted because only public facts should be shown not speculation.	Comment noted, but no changes made. To expect that PFHxS would be working by the same mechanisms as the shorter and longer chain PFSA and PFCA is a reasonable assumption, when these are so clear in their ability to affect certain detailed mechanistic endpoints.
Japan	21	Section 2.2.4	Article 2.4.4 **Mixture toxicity and combined effects of multiple stressors** should be deleted because it is not appropriate to discuss in combination with other subsrances or stressors. Only the toxicity of PFHxS, its salt and related compounds should be described.	According to Annex E criteria (b) of the convention "Hazard assessment for the endpoint or endpoints of concern, including a consideration of toxicological interactions involving multiple chemicals" hence this sub-section is within the scope of the convention.
Japan	22	100	Data of degradation of PFHxS should be described. This conclusion that PFHxS does not degrade is bassed on general properties of PFAS. Judgement should be done based on scientific data.	The conclusion made here is established and applies to PFAS in general.

Combined responses to late comments on 1th and 2nd draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS) and its salts and PFHxS-related compounds

Source of Comment	Page	Para	Combined comments on the 1th and 2nd draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
USA	3	3	Is this the peak production ? Perhaps an average annual production rate will be more informative, to provide an estimate of how much is in the environment.	The information that we have on production is discussed in Chapter 2.1. We have reached out to 3M and requested information on historical production, but they have not given any further information.
USA	3	5	The edible portion of fish is rich in protein so why would it be excreted rapidly ?	Text has been modified for clarification.
USA	3	5	The long-chain PFAAs are also accumulated in the liver. Has a mechanism been proposed for the rapid excretion through gills ? Is tihis unique to PFHxS or general to all PFAAs ?	To our knowledge no mechanism has been proposed and it does not only apply to PFHxS (also mentioned for PFOA).
USA	3	6	What are the volatile precursors? I did not think the sulfonate family derivatives were particularly volatile.	There is no concrete list of volatile PFHxS-precursors but precursors of PFOS and PFBS have been detected in air.
USA	3	6	Not sure of specific volatile precursors, but Scott Mabury's group demonstrated atmospheric transport of these chemicals, which explains their presence in the Arctic.	See above.
USA	3	6	Isn't transport by nonair-routes, e.g. ambient and waste water also possible routes for distribution?	Yes, the majority of PFHxS is probably transported by ocean currents. However, air transport has also been detected. See Section 2.2.4. for details.
USA	3	6	PHxSA: Check accuracy of acronym.	The acronym used in Buck et al 2011 is used in this document which is also the acronym most frequently detected during the PubMed search.
USA	3	7	Add "respiratory and oral" uptake from dust	Text has been added.
USA	3	7	Use 35 years as longest half live: There is an older study with a longer half life. The longest half life in the literature is 35 years for males and females. See Zhang, Y., S. Beesoon, L. Zhu, and J.W. Martin. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ. Sci. Technol. 47:10619-10627.	35 years and reference added
USA	4	8	Edit sentence: PFHxS binds to the thyroid transport protein, and has been associated with changes in serum thyroid hormones across species.	Text has been edited.

USA	4	13	POSF….. Check accuracy of acronym.	Acronym used in Buck et al 2011 is used in this document which is also the acronym most frequently detected during PubMed search.
USA	4	13	Would these compounds environmentally degrade to sulfonates. I would think the S-F bond might also be a strong bond.	It is the derivatives of PFHxSF (raw material) that are used in products and that degrade to PFHxS.
USA	5	Figure 1	Are these the only salts available?	No these are examples. A full list of compounds is given in the INF document.
USA	6	Table 2	Seems to be rather high. For PFOS we found K_{OW} as not measurable based on EFSA and ATSDR	Text has been added based on comments from other Parties as well.
USA	15	51	Did they look at milk as an excretory pathway for pigs ? If they were not lactating, that excretory route would not be active and one would expect less excretion.	No, they only looked at urine and feces excretion.
USA	18	68 2nd 73	Comment to serum level 1700 ng/ml " This number seems high to me. The highest value I have seen is 17 ng/mL (17 ug/L). See Olsen et al. 2017. Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000–2015"	Comment noted, and reference was added. This is a study from Sweden, and the high serum levels were observed in a person living in the area receiving PFHxS contaminated tap water for 35 years.
USA	18	68 2nd 73	Comment to "Levels in plasma range from <0.05 – 80 µg/L" - Check this top range. Again, 17 ug/L is the highest I have seen.	Information was from ECHA 2017a, but we were not able to find the original reference so the range in plasma was deleted.
USA	18	68 2nd 73	Birth cohort Citation?	These birth cohorts were from Bjerregaard-Olesen et al., 2017 as included in the end of the sentence.
USA	18	68 2nd 73	Comment to Fisher 2016 - While this may be the newest epi sudy, it is not likely the best one, and the results appear to be reported inaccurately. In the Fisher paper PFHxS was negatively associated with increasing parity, negatively associated with increasing maternal age, and negatively associated with mothers from foreign born countries. These are the only significant effects for PFHxS from the Fisher paper. Other potentially better choices for epidemiology- Vélez, M.P., T.E. Arbuckle, and W.D. Fraser. 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. Hum. Reprod. 30:701-709.	This piece of information was removed to reduce some details.

			Taylor, K.W., K. Hoffman, K.A. Thayer, and J.L. Daniels. 2014. Polyfluoroalkyl chemicals and menopause among women 20-65 years of age	
USA	19	Chapter 2.4.1	May need a brief mention of toxicokinetics, data available for rat, mouse, monkey and humans. May wish to highlight major species differences in elimination rate and gender differences, consistent with other PFAS (see Sundstrom et al, 2012, Reprod Toxicol 33 :441-451).	This has been mentioned in the text connected to some of the results that are highly impacted by the differences in toxicokinetics, and also elaborated on in the bioaccumulation chapter.
USA	19	Chapter 2.4.2	Suggest adding a section on reproductive and developmental toxicity in animals- i.e. Butenhoff et al. 2009.	A paragraph has been added for developmental toxicity.
USA	19	77 2nd 88	Add " There were also significant decreases in red blood cell counts, hematocrit and hemoglobin concentrations".	These data has been included in a separate paragraph (no.90 in draft 2).
USA	19	78 2nd 89	May wish to include papers by Wolf et al, (2012, Reprod Toxicol 33 :546-551, and Rosen et al. (2013, Toxciol 308 :129-137) to compare these effects of PFHxS to other PFAS (relative potency). In general, it will be informative to compare the effects of PFHxS to other prominent PFAS such as PFOS, PFOA).	No text added in this version of the RP. We will consider it in the final version as we do agree that such table would be informative.
USA	19	78 2nd 89	May wish to include Watkins et al (2015, Mol. Cell. Endocrinol. 400:90-101) that described the strongest effects of PFHxS (among PFAS evaluated) on adipocyte differentiation and function.	Text has been included.
USA	21	89	There are a couple of new studies on this topic for your reference (Preston et al., 2018, EHP, 126 :027013 and Ramhoj et al., 2018 Tox Sci, in press)	Thank you, both has been included in the RP.
USA	20	80 2nd 91	Suggest stating all doses tested. Apply to all animal studies.	Text has been edited.
USA	20	80 2nd 91	Reporting the LOAEL is considered to be more informative (or report both).	Text has been edited.
USA	20	82 2nd 94	Should it be potentiation instead of potential	Yes, text has been edited
USA	23	94	Should this be « similar potentiation to » or (alternatively) « potentiation levels similar to those seen with »?	Text has been edited, hopefully potency will cover both dose and response similarities.
USA	19	78 2nd 96	Rewrite the sentence with Nelson et al 2010	Text has been edited
USA	23	98	Comment to HDL in Fisher et al., 2013 " Check this. I don't think there was a strong association with HDL. The results	Text has been rewritten.

			presented for this parameter could have been based on the unweighted model. Weighted results were adjusted for the probability based sampling strategy while the unweighted results may be biased in that they do not adjust for the complex survey design. From the weighted model: β = -0.004 (95% CI: -0.02, 0.016). There is no association with HDL according to the weighted model"	
USA	23	78 2nd 98	Comment to Fisher et al., 2013 " It might be worth mentioning that in this particular study no associations were found between PFOS and any of these parameters."	Text has been edited.
USA	23	78 2nd 98	Suggestion for rephrasing: "was higher than the 2014 value from the NHANES (2017) monitoring in the United States (1.35 µg/L) ~~were slightly higher than in a study performed on data from The National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States (Nelson et al., 2010) and the PFOS and PFOA levels were slightly lower~~	Text has been rewritten.
USA	23	78 2nd 98	Comment to Nelson et al., 2010 " In the same paper, PFOS was associated with decreased total cholesterol and non-HDL."	Text has been amended to include the comparisons with PFOA and PFOS too, but increases in those two PFAS were associated with an increase in TC and non-HDL.
USA	23	78 2nd 98	Suggestion for rephrasing: "Study using 2003–2004 plasma concentrations of 7 PFAS there was a positive association with HDL cholesterol for 6 of the PFAS including PFHxS. (Starling et al., 2014). From the paper : PFHxS was associated with an increase in HDL cholesterol : 1.46 (95% CI: 0.19, 2.73).	Numbers of PFAS positively associated with HDL cholesterol was changed to 5 (both PFOA and PFHpS 95% CI covered 0 and were thus excluded, resulting in 5 PFAS). Text has been shortened and details have been moved to the INF-doc table 3.1.
USA	23	78 2nd 98	Comment to Starling et al., 2014 "Disagree. The confidence intervals include zero for TC."	Sentence has been rewritten to avoid misunderstanding. PFOS was associated with an increase in TC: per ln-ng/m Ll 8.96 (95% CI: 1.17, 16.22)
USA	23	78 2nd 98	Comment to Starling et al., 2014 "From the paper : PFHxS was associated with an increase in HDL cholesterol: 1.46 (95% CI: 0.19, 2.73). "	Comment noted beta value included in INF-doc table.
USA	24	99	Comment to Wen et al., 2013 "Free T4 was the only association that was demonstrated in men. The study as a whole demonstrates that associations with thyroid parameters are stronger in women than in men".	Text has been amended.
USA	24	99	Comment to Chan et al., 2011	Text has been edited.

			" The confidence interval includes 1.0, so no association. From the abstract: Analyses by conditional logistic regression indicated that the concentrations of PFAs in this population were not associated with hypothyroxinemia among pregnant women. The current findings do not support a causal link between PFA exposure and maternal hypothyroxinemia in the studied population."	
USA	24	99	See previous comment. There is no association because the CI contains 1.0	Text has been edited.
USA	24	99	Comment on Shah-Kulkarni et al., 2016. "PFHxS was only positively associated with T3, and only in females. PFOS was not associated with any thyroid-related parameter."	Text has been amended.
USA	24	100	Comment on Stein and Stavitz 2011. " Interestingly, no strong associations with ADHD were seen with any of the other PFAS that were analyzed."	Text has been amended.
USA	24	100	Comment to Hoffman et al., 2010 " Both PFOA and PFOS were also positively associated with parentally reported ADHD."	Text has been amended.
USA	24	101	Suggest adding 'measles, rubella, tetanus, and influenza.'	Infectious diseases included are mentioned in the text.
USA	24	101	Comment on "Q4 vs. Q1 OR: 1.55, 95% CI: 0.976, 2.45; p for trend=0.045" -This is not a significant relationship because the CI includes 1.0. In this paper no strong associations were found for PFHxS or PFOS.	Comment noted, however p for trend was significant.
USA	24	101	Comment on Granum et al., 2013 " Similar results were seen with PFOS."	As far as we understand similar results were seen with PFOA, which has been included in the text.
USA	24	101	Comment on Grandjean et al., 2012 " Check numbers. Is this an association with maternal serum levels or child serum levels?"	"at age 5" has been included.
USA	24	101	Need to also state that many of these studies found similar findings for other PFAS. Most participants had multiple PFAS present in bloood or serum.	Text has been edited.
USA	24	101	From Timmerman et al. (2017). A doubling of serum PFHxS at age 13 was also associated with reduced odds of asthma at age 13.	Text has been edited.
USA	24	102	Comment to Jensen et al., 2016 "PFOS was not associated with increased odds of miscarriage either."	Text has been edited
USA	24	103	Comment to Khalil et al. 2016 " What variables were controlled in this analysis? In at least one study PFOS was high in bone. Was PFHxS the only PFAS examined in this study? "	Text has been edited.

USA	25	107	It is important to indicate the cases where there were a number of PFAS materials in the blood and more than one appeared to demonstrate a significant association with the parameter being monitored, not simple PFHxS.	Comment noted and text amended with details in several places in the chapters reflecting biological effects.
USA	25	107	There are not too many mixture studies available, but **one** in vitro study evaluating interaction between PFAAs and BPA suggested synergissm (Zhou et al. 2017, Chemopshere 178 :378).	Thanks for providing the study, it can be good to be aware of it since it gives some support to the observations from the new study from Ramhøj et al 2018. However, since it includes PFOA and PFOS as PFAS and not PFHxS, it will not be included in the RP.
USA	25	107	It is important to indicate the cases where there were a number of PFAS materials in the blood and more than one appeared to demonstrate a significant association with the parameter being monitored, not simple PFHxS.	The text has been significantly edited since draft 1.

Comments to the 2nd draft

Source of Comment	**Page**	**Para**	**Comments on the second draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds**	**Response**
Canada			General comment: Overarching comment on "read-across approach" to support the risk profile for PFHxS : It is suggested that the Risk Profile would be strengthened by including the approach that has been adopted on how and when data on analogous substances are to be used. Data from analogous substances are cited, notably from PFOS and PFBS. In the absence of an approach, the readers are invited to apply their own interpretation, which may vary, creating debate as to the relevance and applicability of the read across information presented. For instance, in paragraph 86, it is stated that available studies comparing toxic effects of PFBS and PFOS in aquatic organisms indicate that toxicity increases with increasing carbon chain length. (Giesy et al., 2010). Assuming this is the basis of utilizing read across information, it may be worthwhile to state this assumption within the context of utilizing read across. On the other hand, data cited in paragraph 86 from Lou et al., 2013, indicate effects were	Agreed. Text has been included (in Introduction) to describe how and when the read-across approach is used in the document, it is mainly for persistence See amendments/clarification in specific sections where read-across is applied. For the adverse effect Chapter we have used results from studies on PFHxS as far as possible. However, due to the limited number of studies of PFHxS on aquatic organisms, information from studies that included both PFOS and PFBS has been referred. We also included one new study on PFBS to show that chronic transgenerational effects has been observed also for this compound which in other experiments has shown lower potential than PFOS to induce effects. The aquatic toxicity section has further been considerably rewritten. For the Lou et al., 2013 study, both PFOS and PFBS changed the expression of sex-hormone receptors in

			observed resulting from PFOS exposure, while no effects were observed from PFBS exposure. In paragraph 96, effects were noted by Corsini et al., 2012 in exposures to both PFOS and PFBS. These two examples may help establish a framework to explain the use of read across information. Where effects exists for both PFOS and PFBS, which can be viewed as boundary substances to PFHxS in terms of carbon chain length, it may be reasonable to infer that a similar effect is elicited by PFHxS, although assigning a median effect concentration may be challenging. Other considerations can also include a statement, when appropriate, where a read across approach is even more limitative such as for ecotoxicity data due to sparse toxixity results and the species-, gender- and chain length-dependency. Furthermore, in the absence of having results for both PFOS and PFBS, there is an absence of support for asserting that a similar effect would be elicited by PFHxS. In the examples provided earlier, Lou et al. observe an effect from PFOS exposure, but none for PFBS. Consequently, assigning similar behavior to PFHxS is difficult to support. Use of read across information by interpolating between similar substances is a useful and legitimate technique in risk assessment, particularly when dealing with relatively data poor substances. By articulating a framework as to when and how read across information is used, and citing data that falls within this framework would strengthen the risk profile for PFHxS.	the brain and liver, but only PFOS exposure gave histopathology changes in the liver. The Corsini et al., 2012 provide mechanistic support to the human epidemiology studies on immunology effects as several PFASs with shorter and longer fluorinated chains as well as different side-groups all affected responses important for immune responses to infections.
Canada	3	6	PFHxS was found in air at Alert (Canada) and Zeppelin (Svalbard). Reference already included in the references section: Wong F, Shoeiba M, Katsoyiannis A, Eckhardt S, Stohl A, Bohlin-Nizzetto P, Li H, Fellind P, Sua Y, Hung H (2018). Assessing temporal trends and source regions of per- and polyfluoroalkyl substances (PFASs) in air under the Arctic	Text has been edited.

			Monitoring and Assessment Programme (AMAP). Atmospheric Environment 172 (2018) 65–73.	
Canada	6	Figure 1	Suggest to replace "Precursor/start material" in description of substance b) with "PFHxS-related compound" for consistency.	Text has been edited.
Canada	8	21	Suggested changes to ensure accuracy of the Canadian Domestic Substance List purpose.	No changes made. According to our search on the DSL we find a number of PFHxS related substances on the list (see Table 13 in INF document). Have these PFHxS-related compounds been removed from DSL recently?
Canada	14	Section 2.2.3	Suggest, as per the toxicity section, to separate between aquatic organisms and terrestrial mammals (including humans). This approach has been taken in other risk profiles such as in the risk profile for PFOA.	This request was denied in the previous round of comments. Further, it has not been raised my any other party/observer. For the amount of time this will take to edit, we do not see what this change will significantly add to the discussion on bioaccumulation.
Canada	18	73	1. In a study on PFASs in herring gull (*Larus argentatus*) eggs collected in 2012–2013 from 19 Canadian and U.S. colony sites across the Great Lakes, PFHxS was detected in >97% of the gull eggs and at concentrations of 1.44 ng/g ww or less in 98% of the measurable samples (Letcher et al., 2015). Two colony sites, Gull Island (Lake Superior) and Monroe (River Raisin at Lake Erie), showed relatively lower PFHxS concentrations (<MLOQ in 100% of egg samples) compared to other colony sites. In Caspian tern or herring gull eggs collected in 2013-2014 from 6 colonies in the area of St. Mary's River or Saginaw Bay in the Great Lakes (Su et al., 2017), the PFHxS concentrations were similarly low as reported for the gull eggs from the Letcher et al. (2015) study.	No text added in the RP The data is listed in "UNEP/POPS/POPRC.14/INF/[…]"]
Canada	24	Section 2.4.4	There are several citations of data that are generated on mixtures and combined effects on multiple stressors (e.g. paragraph 98, 105-109, 117, 120). It may be of use to be selective in reporting such results where effects cannot be attributed to PFHxS alone. For example, in paragraph 97, testing was conducted where test system was dosed with a mixture heavily weighted to PFOS compared to PFHxS (91% vs 3.8%). It is	We moved the para 97 to 2.4.4 Mixture toxicity and combined effects of multiple stressors, since these studies did not correlate with levels of PFHxS alone, but looked at effects correlating with combined PFAS level, and thus fit better into this chapter. For the human epidemiology studies, (as well as ecotoxic effects observed in field studies) the effects observed could indeed be a result of the combined effect of multiple stressors.

			not obvious in this case that the results can be attributed to PFHxS. It is suggested that a statement be provided indicating the weight that should be attributed to such evidence.	However, although some of the studies did include multiple pollution in their analysis, most analysis was done as weighted analysis against one compound at a time. The field and human studies are further supported by controlled experimental data. An opening paragraph for the human epidemiology chapter 2.2.3 describe some of the general limitations with those studies, and two tables were provided to sum up the design and outcome of some of the epidemiology data in the INF-doc.
Canada	27	Table 6	• Detection in top predators in Arctic with increasing levels further away from local sources (Letcher et al., 2018; Routti et al., 2017; Tartu et al., 2017b; 2018). Detection in fish-eating birds (gulls and terns) from the Great Lakes and close to sources (Letcher et al., 2015; Su et al., 2017)	Letcher et al 2018 added to the table. Letcher et al 2015 and Su et al 2017 is not detection due to long-range transport and do not belong in the now Table 5.
The Netherlands		General	The Netherlands appreciates the work done by the drafters of the Risk Profile for PFHxS. The Netherlands wishes to contribute to the further development of this Profile by providing some comments below.	Comment noted.
The Netherlands		General	Together with PFOS and PFOA, PFHxS is one of the PFCs most appearing in environmental or human monitoring data. The available data suggest that marketed volumes of PFHxS are or have been up to a factor of 10 lower than those of PFOS and PFOA (see for instance Sundström et al 2011). Literature also indicates that on a lot of places concentrations of PFOS and PFOA are decreasing, whereas PFHxS is levelling off. Land et al 2018 - Temporal trends of perfluoroalkyl acids in humans and in the environment: "In regions where regulations and phase-outs have been implemented, human concentrations of PFOS, PFDS, and PFOA are generally declining, while previously increasing concentrations of PFHxS have begun to level off." This trend could be better reflected in the risk profile.	There are some discrepancies in the trend data both from environment and for human data and we have tried to reflect this in the document. Some newer data show increasing trends see: Section 2.2.4 A recent study reporting significant increase in concentations of PFHxS ($p<0.006$) during the period 2009 - 2015 in arctic air both in Canada and Norway indicating that an increase in long-range transport has occured (Rauert et al., 2018). Information from Land et al., 2018 has also been included in 2.3.1 and 2.3.2. We did not include the data from Sundstrøm et al 2011, but instead used the data from Nyberg et al., 2017, which covered a longer period from the same area, in the paragraph 80.

The Netherlands	3	2	The PFHxS risk profile summarizes in paragraph 2 the knowledge of the use of PFHxS with the following sentence: "2. PFHxS, its salts and PFHxS related compounds are or have been widely used in fire-fighting foams, as surfactants, in metal plating as well as in cleaning, waxing, polish and other surface treatment products, and/or water- and stain-protective coatings for carpets, paper, leather and textiles." In the Norwegian Environment Agency Report M-961/2018, cited in paragraph 28 of the risk profile, the conclusion on page 18 states: "Across all sources, it was found that there is in general a lack of information on the quantitative production levels and regarding descriptions of product specific uses of PFHxS and related substances in the public domain." This is quite a different conclusion than the message provided in paragraph 2 of the risk profile. The Netherlands would like to know whether there is a clear picture of the applications of PFHxS and the amounts used and if these data are available, can they be provided in the risk profile? If not, we would recommend to take the conclusion in the report of the Norwegian Environment Agency as a proper one to communicate in the summary of the risk profile and to convey that message as well in the remaining part of the profile, e.g. in paragraph 32. Following above, the dossier contains a limited information on the amounts PFHxS produced and the applications in which it is used. Data provided (paras 3, 13, 27, 29, 35, 40 and 29) do not enable to come to a comprehensive picture, but suggest amounts of a few tonnes up to 1000 tonnes/year (China). The European annex XV dossier and the RMOA on PFHxS indicate: 'At present there is no available data on the production and use of PFHxS globally or in the EU.' The dossier would substantially be improved if the authors indicate the range of production based on the data provided and the uncertainty in these amounts. The fact that production within the European Union still takes place (Italy is mentioned in para 29), but that until now PFHxS is not registered under REACH is a fact	Regarding comment on production and use in paragraph 2 in the executive summary it is a summary of information and represents both historical use and what we know about the percent use. During the analysis of the market research reports and the survey among stakeholders (presented in Norwegian Environment Agency Report M-961/2018) we did contact a number of producers, users and companies that offer these compounds for sale, with very few results. The market research report provided some information of varying quality but the stakeholder survey gave basically no results. The contacted companies either refused to answer, hang up when approached by phone (native speaking) or told us they would get back to us (which they did not do). A number of companies also replied that they did not sell/produce/use these substances even in the cases where they offer them for sale on their web page. Miteni in Italy has also been contacted both in English and Italian but they have no willingness to answer any questions. Hence, there is no clear picture of the applications of PFHxS and the amounts used and we have not been able to find good data so far. We have observed that the registration under "Hazard classification & labelling, C&L Inventory" under REACH has increased since the nomination but to our knowledge (as of today) we do not know about any registrations under REACH. On the other hand we do not think that the industries lack of willingness should benefit them in any way and we hope that at some point the industry or their branch organisations understand that will benefit from releasing information. Regarding the conclusion of the report from Norwegian Environment Agency (Report M-961/2018) we are reluctant to use the conclusion from the report in the risk profile, as we express in section 2.1.1 the quality of the market

			worth mentioning, taking into account that registration by the Italian producer is still possible until June 1, 2018. If not, the production in Italy is below 1 tonne per year or might even have ceased. Insight would also be improved if the amounts are provided in the broader picture of PFC production in use, e.g. by comparison with PFOS and PFOA. The time trend described in Norwegian Environmental Agency (2018) coincides with the trend described in Land et al 2018 and the time trend in human milk in Sundström et al 2011.	research reports are questionable and definitely did not cover a global market. It is too early to conclude on the amounts produced of PFHxS, its salt and PFHxS-related compounds. According to submissions and comment by China they are surveying the production and use. Hopefully they will be able to put some light on this in the future.
The Netherlands		General	Do the authors have any idea on the amounts of PFHxS intentionally produced and applied and the amount being present in mixtures of other PFCs? Furthermore the dossier could be improved by providing information about the concentrations of PFHxS for a number of uses.	See answers to questions above.
The Netherlands		Section 2.2.3	The Netherlands supports meeting the bioaccumulation criterion. In our view the use of BMF and TMF data from literature is not the best way to support that criterion and can be handled in a more critical way. In quite a number of references liver concentrations are devided by whole body concentrations with relatively high values as a result. For a discussion on the topic we refer to the article of Franklin (2016), IAEM 12(1): 6-20. Half-life seems to be a better proof of bioaccumulation potential as indicated in Franklin (2016).	Regarding the bioaccumulation criteria, the uncertainties of some of the studies was discussed in the nomination dossier. And in the case of PFHxS the various data presented (BMF, TMF and degradation half-life, monitoring data) all together suggest that the B-criteria under Annex D is met. However, some text and references have been added.
Japan	5	11	PFHxS salt should be described precisely separated from PFHxS related compounds because PFHxS salt does not degraded into PFHxS.	No changes made. According to the report (M972/2017, page 9) "All PFHxS salt will eventually dissolve in water resulting in the release of PFHxS.
Japan	5	15	Scientific data should be described to conclude that each chemical substance listed on the PFHxS-related compounds is decomposed into PFHxS. The data would be apprecied to be provided before preparing the final draft.	Comment noted. This subject is answered other places in the comment table.
Japan	7	19	It seems to include no-pure reviewed article in the reference list such as review articles and the data reports.	See answer to comment from Japan on first draft.
Japan	8	24	Regulation of the raw material PFHxSF will be enough to control the related compounds.	Comment noted. The nomination included PFHxS, its salts and PFHxS-related compounds including PFHxSF.. A number of parties to the Convention requested at POPRC13 to include a non-exhaustive list of compounds to

				explain which compounds are included.
Japan	9	28	Conclusion must be done based on scientific data which are publicly available. Confirmation of the reiliability of the results and proper judgement can not be done without the evidence for the risk assessment.	Conclusions are made on available data. Unfortunately, producers globally refuse to release production and usage data. A number of producers have been approached (in their native language) but they do not want to release data. It is the industry that holds back this information.
Japan	12	39	In this paragraph, there is no reference information as the basis for explanation. The references should be added.	We have highlighted the references in yellow: they can be released at their production, at their assembly into a commercial product, during the distribution and industrial or consumer use, as well as from waste treatment facilities such as landfills and wastewater treatment plants (Shafique et al., 2017), including from land treatment using contaminated sludge from wastewater treatment plants. Studies indicate that PFHxS remain relatively unchanged throughout the successive treatment steps (Kunacheva et al., 2011, Thompson et al., 2011). Furthermore, PFHxS-related compounds may be transformed to PFHxS in the environment and biota (for details, see section on PFHxS precursors and degradation below).
Japan	13	45	There is a lack of information as the basis for deriving such a conclusion. As Dr. Takatsuki pointed out, read-across should not be used.	To our knowledge there was no decision made at POPRC13 that read-across should not be used. In fact a number of Parties have suggested more use of the read-across approach and to make it clear in the draft RP that this has been done.
Japan	13	45	It is to be deleted because it is just general opinion, not data Since the stability of PFSAs is in general based on the stability of the fluorinated carbon chain, it can also be concluded for PFHxS that no biodegradation can be expected in water, soil or sediment.	The paragraph has been edited and reference added.
Japan	13	45	Sufficient data of similarity are not shown to apply read-across appoach.We would like to delete this sentence because we understand at POPRC13 read-across approach will not be used for Risk Profile.	Text has been edited and references added.
Japan	13	46	There is a lack of reference information on the basis for deriving such a conclusion:	Data has been added and read-across has been used - see response above.

			Furthermore, based on a read-across approach, conclusions applied to the persistence of other PFASs such as PFOS and perfluorobutane sulfonic acid (PFBS) can be anticipated to be valid for PFHxS as well	
Japan	13	47	It is appropriate to confine the scope of the PFHxS-related compounds to its salts, esters, halogenide such as F or Br on the end, however evidence is insufficient to regulate any compounds that include C6F13SO2 group. More data would be necessary to widen the scope of PFHxS compared to PFOS.	Data has been added and read-across has been used.
Japan	13	47	There is no explanation why these conclusion is drawn out. The evaluation should be based on experimental data Based on available data on the degradation of PFBS- and PFOS-precursors, PFHxS precursors are anticipated to degrade to PFHxS in the environment	Data has been added and read-across has been used.
Japan	16	60	Although this paper described that PFHxS precursors could be degraded by biological degradation, the compounds can not be degraded in the atomosphere or open water since these kind of compounds degraded under the anaerobic condition as described in the references.	The references used in this paragraph review the different possible routes of transport. There are no conclusions on transport made in this paragraph of the risk profile.
Japan	25	112	We would like to delete this sentence because we understand at POPRC13 read-across approach will not be used for Risk Profile.	See earlier comments above on the use of the read-across approach.
Japan	26	112	Miscell formation should be described for the reason.	See earlier comment above on same subject.
Japan	26	Table 6	There is no description on the chemical identity. The other chareacteristics of PFHxS it self is proper, but no comment on the PFHxS-related compounds.	Table 5 summarizes the POP characteristics of PFHxS. The chemical identity is described elsewhere.
Japan	28	120	The conclusion on PFHxS and its salts is adequate, but that on the related compounds has lack of data and logical leap. We should think this part should be deleted: PFHxS related compounds are likely, as a result of their long-range environmental transport, to lead to significant adverse human health and environmental effects such that global action is warranted.	No changes made. We have made this conclusion based on the evidence summarized in the RP. It is up to POPRC to decide on this conclusion.
POPRC member 1	3	5	Based on the identified protein bioaccumulation mechanism rather than lipid partitioning standard BCF/BAF are less meaningful descriptors for	Text has been edited.

			bioaccumulation for PFAS including PFHxS. Biomangification with BMFs and TMFs >1 (BMF range 1.4–373 and TMF range 0.1–4.3) was demonstrated for PFHxS, including from the Arctic food chains. The estimated serum elimination half-life of PFHxS in humans is higher than other PFASs and varies from 5.3 to 14.7 years.	
POPRC member 1	3	7	Is it possible to include time trend information ? This is important and should be inlcuded in the summary.	Information about trend in human serum has been included in the summary.
POPRC member 1	5	12	Based on the length of the Risk profile I would suggest to delete para 12 and 13. *Reason*: A detailed information on use is presented in chapter 2.1. A summary on use is presented in para 2 of the Executive summary. So the information is best located in these sections of the report. Please provide a more in-depth reasoning why PFHxS-related compounds are included in the evaluation and give examples	Introduction is shortened. Text on why PFHxS-related compounds are included has been added. A paragraph has been included to justify the use of read-across in this document.
POPRC member 1	5	13	Please see comment above. This information refers also to expected production volumes from one country which is best embedded in the overall evaluation on production given in chapter 2.1	Text has been deleted
POPRC member 1	5	14	Including branched isomers ?	Yes in theory, but we have not identified any CAS No. in our report M-792/2017. Every substance that contains this moiety $C_6F_{13}SO_2$- is included.
POPRC member 1	5	15	If fluorinated polymers that contain the perfluoroalkyl moiety mentioned in b) are also within the scope this should be clearly included in the definition.	Some of the CAS Nos. that we have identified refers to polymers
POPRC member 1	5	15	What about the cyclic forms of PFHxS (salts) ?. E.g. CAS No 68156-01-4 or CAS No 3107-18-4. Please consider/mention the cyclic compounds in the text on chemical identity.	None of the CAS Nos have this moiety, $C_6F_{13}SO_2$- so we don't consider them as included.
POPRC member 1	6	Table 1	Is this mixture still in use/production? Main component is Potassium heptadecafluoro-1-octanesulfonate, so this is not a trade name for PFHxS but rather an impurity/by-product as mentioned in para.25. It is assumed that 3M phased out their perfluorooctyl-based chemistries in 2002.	No changes made: We do not know what is still in use or produced. RM70, RM75, and RM570 are trade names for PFHxS-related compounds.

			It would be good to have additional actual trade names for PFHxS or related compounds in this column.	
POPRC member 1	7	Table 2	Should the * also apply to Log Kow estimate ?	Table 2 has been edited by Dr. Wang (ETHZ, Switzerland).
POPRC member 1	8	21	Para. 21 only lists national regulations and measures, eiter delete or change the heading. Please include SAICM : http://www.saicm.org/EmergingPolicyIssues/Perfluorinatednbsp;Chemicals/tabid/5478/language/en-US/Default.aspx	Text has been edited.
POPRC member 1	8	24	Add this text: Of the PFHxS impurities from the 3M ECF production process for PFOS also branched isomers of PFHxS were detected e.g. 18% branched from 4.7% PFHxS impurity in one lot (Benskin et al. 2010).	Text added.
POPRC member 1	8	25	Is telomerisation a production process relevant for PFHxS chemistry?	No. Telomerisation isn't relevant for PFHxS chemistry.
POPRC member 1	8	25	What about N-MeFHxSA or N-EtFHxSA sulfonamidoethyl acrylates and methacrylates ?	Acrylates and methacrylates are reaction products of N-Me/N-Et FHxSEs. So it's included in the sentence here.
POPRC member 1	8	25	Building blocks: Please quote the reference	The reference is 3M, 1999, which was mentioned above in the same paragraph. Reference added in text.
POPRC member 1	9	Table 4	This table should be moved to the INF Document.	The table has been moved to INF.
POPRC member 1	11	31	Applications are already mentioned in the previous lines, please merge this information. Intermediate feedstock for … ? Please specify	Text has been edited. No further information regarding the use as "intermediate feedstock" was revealed in this study.
POPRC member1	11	34	Please explain what impact is expected from this SNUR.	We not entirely sure. It's considered a SNUR, then there should be no legal requirement on the production/import/use of this salt in metal plating, but this may need to be clarified by the US EPA.
POPRC member 1	12	39	Add the following sentence: However source identification for PFHxS in groundwater samples (n=102) from non-industrial areas and drinking water in U:S. (n=36977) showed that PFHxS clustered/occured together with PFOS. Thus PFHxS might originate from similar sources such as e.g. AFFF, pesticides applications, (fluoropolymer) manufacturing, landfills and WWTP	Sentence added with some minor changes.

			effluent (Wei et al. 2018, Guelfo and Adamson, 2018).	
POPRC member 1	12	39	Which treatment steps are meant ? Waste water treatment ?	Yes, wastewater treatment steps.
POPRC member 1	13	45	The read-across approach should be further documented and described. Though developed for REACH the RAAF can give useful elements to justify the applied read-across. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf	Text on read-across has been added to the introduction. It is also clearly stated in the document where the read-across approach has been applied.
POPRC member 1	13	45	Please explain the vP criteria in the text	Text added and a link to where to find a full text about the criteria under REACH is added.
POPRC member 1	13	46	PFBS is not mentioned in the previous para for read-across. No detailed data on persistence related to PFBS is presented therefore the information for read-across is insuficient.	Text and references has been added.
POPRC member 1	13	2.2.2	Some of the paragraphs are not related to degradation but do also cover uses and exposure, therefore renaming of the section is suggested.	Heading has been changed.
POPRC member 1	14	50	Could you please explain what is biological and abiotic leaching ?	Text has been added for explanation.
POPRC member 1	15	53	It should be made chlear if BMFs are dietary/lab or monitoring based. The Preliminary GD for evaluation/WoE for bioaccumulation can be useful for this section : http://chm.pops.int/Portals/0/docs/from_old_website/documents/meetings/poprc/POPRC3/POPRC3_Report_e/POPRC3_Report_AnnexVI_e.pdf	Text has been edited and reference added.
POPRC member 1	16	57	Species specificty is already mentioned in the previous para. Cf. highly expressed in Sundstrom et al. 2012. So please rephrase the sentence.	Sentence has been deleted.
POPRC member 1	16	57	Not clear, cf. the following para. stated that tissue distribution is similar in humand and other mammals.	No changes made. It is stated that the distribution is similar in terms of which tissues PFHxS is detected – not identical.
POPRC member 1	16	58	Excretion is already mentioned in para. 56. So either merge the information or delete it.	Text has been removed to avoid duplication.
POPRC member 1	16	61	Not clear why this information is relevant for LRT ? This information should be moved to 2.1.3.	Text has been edited to better explain what is meant.

POPRC member 1	17	68	Please add the geographic area or location.	Added.
POPRC member 1	18	69	Please add the concentration levels	Concentration added.
POPRC member 1	18	70	Local areas can also be influenced from local sources, so please further explain why levels in these local areas do originate from LRT.	Text has been rewritten to avoid misunderstanding of the meaning of a local area.
POPRC member 1	18	70	Including PFHxS ?	The section reflecting the Routti studies has been significantly changed and has also been checked by the author herself. Please see new text.
POPRC member 1	18	71	Please quote the correct reference if it is not Routti et al.	The section reflecting the Routti studies has been significantly changed and has also been checked by the author herself. Please see new text.
POPRC member 1	18	73	Please add the countries/regions	Worldwide has been added.
POPRC member 1	18	74	Please include major findings from EFSA (2012) page 32 that based the assessment on 54,195 analytical results obtained for 7,560 food samples in Europe. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2743	Data has been included both in the RP and the INF-doc.
POPRC member 1	18	76	Please note that now results from 4920 public water systems are availalbe (Guelfo and Adamson, 2018, https://www.ncbi.nlm.nih.gov/pubmed/29427949).	Text has been added.
POPRC member 1	19	78	These findings should move to the hazard assessment section	This information was removed.
POPRC member 1	19	80	Please insert: " However after the first six months infants serum concentrations increased 4- to 3.5-fold for PFOS and PFHxs in relation to cord blood (Fromme et al. 2010, Winkens et al. 2017)." https://pubs.acs.org/doi/abs/10.1021/es101184f https://www.sciencedirect.com/science/article/pii/S2405665017300033	This information was included, as were the references.
POPRC member 1	19	80	Please see also the information given in Winkens et al. 2017 : PFOS and PFOA 3% reduction per month of breastfeeding and for PFHxS 1%.	Information was included, and the reference.

POPRC member 1	19	80	serum or breast milk ?	Breast milk has been included for clarification.
POPRC member 1	20	80	Please give the concentration range	No concentration range was given in the article (only Geometric mean and percentile up to 95), but the text was amended with information from the article that levels were similar to that observed in adults and adolescent.
POPRC member 1		83	Add/move text: "In a recent human biomonitoring study in the city of Ronneby in Sweden people have been exposed to high levels of PFAS via drinking water, including PFHxS (1700 ng/L in 2013) from a nearby military airport. The levels of PFHxS were the highest ever reported in Sweden, (277 ng/mL, range 12–1660) (Li et al., 2018)."	Text has been moved.
POPRC member 1	20	83	Please also quote the decline trend of PFHxS in newborn blood spots by Spliethoff et al. 2008 https://pubs.acs.org/doi/abs/10.1021/es8006244	Study and reference has been included.
POPRC member 1	20	85	Information on half-lives should be compiled in a comprehensive manner in one place in the document. Because also other studies are listed in section 2.2.3 and Li et al. 2018 is already reported there I think it is not necessary to repeat this information here.	Text has been removed.
POPRC member 1	20	Chapter 2.3.2	This section could benefit from a conclusion concerning time trends. This is an important information for the executive summary/Synthesis of information.	Some more studies have been included to describe trend data, and information has been included in the executive summary/Synthesis of information.
POPRC member 1	21	Chapter 2.2.4	According to current chemical risk assessment methodologies please note that findings in this section are also relevant to human health. Please consider that different protection goals have been applied for environmental organisms and human health. So from the information presented below it is not always clear what does it mean in terms of hazard identification for wildlife/population level. Also it would be important to state if the information presented on thyroid organ toxicity is also relevant for humans.	Some structural changes were made to clarify the text.
POPRC member 1	23	99	Please report always the study design of the epidemiological studies because depending on the study designs the provided information differs in quality	Information about study design is provided in INF-doc table.

POPRC member 1	23	100	Please give also the range of the reported values.	Information is provided in the INF-doc table.
POPRC member 1	24	100	Add: ", but no significant association with T3 and T4"	Text has been amended.
POPRC member 1	24	101	Could you please indicate the size of the study group ?	Text has been edited.
POPRC member 1	24	101	Please specify « problematic behaviour », based on … clinical diagnosis ?	Text has been edited.
POPRC member 1		Section 2.4.4	This section and also section 2.4.4. could benefit from findings of Ramhoj et al. 2018 on developmental toxicity in rats. »PFHxS caused no overt toxicity in dams and offspring but decreased male pup birth weight and slightly increased liver weights at high doses and in combination with the EDmix. A marked effect on T4 levels was seen in both dams and offspring, with significant reductions from 5 mg/kg/day. PFHxS can induce developmental toxicity and in addition results of the co-exposure studies indicated that PFHxS and the EDmix potentiate the effect of each other on various endpoints, despite their different modes of action."	Study was included as a new para in Sub-sections 2.3.4. and 2.4.4.
POPRC member 1	24	105	PFCAs findings: how to they relate tof PFHxS mixture toxicitiy. Please justify or delete.	PFCAs should have been corrected to PFAS. However, this study was removed since it had no information on synergy, additivity etc.
POPRC member 1	25	105	Any information on additive or synergistic effects ?	No, study was not designed to investigate that.
POPRC member 1	25	109	Also Germany and U.S have such limits in place, please amend.	Text has been added.
POPRC member 1	25	110	Please include also uses of PFHxS-related substances	Edited
POPRC member 1	25	110	PFAS is normally used for « per- and polyfluoroalkyl substances »	Edited
POPRC member 1	26	112	Please provide information on standard analytical methods for PFHxS in the body text	No changes made. Information on standard methods used are available in the published papers referred to in this risk profile.
POPRC member 1	26	113	2. . Based on the physical properties, PFHxS is known to undergo a protein bioaccumulation mechanism rather than lipid partitioning (UNEP/POPS/POPRC.3/INF/8/2003), which makes standard BCF/BAF analysis less meaningful. Thus comparable to PFOA and PFOS the use of log Kow and BCF have been	Text has been edited as suggested.

			demonstrated to be inappropriate measures of bioaccumulation. Several studies have reported bioaccumulation and biomagnification of PFHxS with field based BMFs and TMFs > 1 for different food chains, including from the Arctic. PFHxS binds strongly to proteins and this phenomenon is observed across species. The reported half-lives of PFHxS in human serum, which is known to be a good indicator of bioaccumulation, is very high (range 5.3–14.7 years),	
POPRC member 1	26	115	Please indicate the regions/countries.	Text has been amended.
POPRC member 1	27	Table 6	Please further justify the read-across, see previous comment.	Reference added in and a description/justification about how read-across is used is added to the Introduction section.
POPRC member 1	28	119	No numbers to show the elevated levels in soil and groundwater are presented in section 2.3.1. It would be useful to incorporate this numbers also in this document and in the body text.	Due to the page restriction of the risk profile most of the data on environmental levels are listed in the INF document. PFHxS does not bind strongly to soil and sediments and are rather water soluble and mobile.
POPRC member 2	3	3	To add the sentence: Current and historical volumes of PFHxS, its salt and PFHxS-related compounds production are unknown;	Text has been edited.
POPRC member 2	3	4	It seems that text where "related compounds" mention should be revised (in brackets);	Text has been edited by other comments.
POPRC member 2	3	5	In the last sentence TMF range (0.1-4.3) does not correspond with the TMFs>1;	No changes made. TMFs>1 are detected over 1 (0.1- 4.3) which fulfils the criteria
POPRC member 2	3	7	Exposure of the general population and breast-fed infants should be shown separately (see p.114);	Text has been modified.
POPRC member 2	3	9	it seems, that toxicity value should be provided (in p.8?) to confirm "toxic to animals including humans"	No changes made to the text, since this is a summary and all the various toxic endpoints are described later.
POPRC member 2	16	59	Regarding Antarctic region PFHxS was found in biota and snow ("UNEP/POPS/POPRC.14/INF/[…]"];	Text has been edited.
IPEN/ACAT	3	2	IPEN believe it is important to highlight this regrettable substitution already in the Executive Summary, and that there is sufficient evidence for this conclusion. The term substitute is used in the same sense as defined in the POPRC Consolidated guidance on alternatives to perfluorooctane	Text has been edited.

			sulfonic acid and its related chemicals UNEP/POPS/POPRC.12/INF/15/Rev.1 “There are several PFSA and derivatives thereof with shorter or longer alkyl chain lengths than PFOS that are used for applications similar to those for which PFOS is used – in other words as PFOS alternatives, though not necessarily safer alternatives. Examples of specific uses as provided in the text below, but this general conclusion is supportted by for example the following references: The Swedish Chemicals Agency simply concludes that ”PFHxS is a shorter version of PFOS” https://www.kemi.se/global/rapporter/2015/report-7-15-occurrence-and-use-of-highly-fluorinated-substances-and-alternatives.pdf “PFHxS is often used as a substitute for perfluorooctane sulfonate (PFOS)” and it may be used in “fire-fighting foams, food contact papers, waterproofing agents and cleaning and polishing products.” https://www.foodpackagingforum.org/news/more-information-on-pfhxs-needed Swedish researchers found that while the voluntary phase out of perfluorooctane sulfonate (PFOS) in 2002 has led to a rapid decrease of PFOS’ and other perfluorinated alkyl acids’ (PFAA) levels in blood serum, PFOS’ substitute perfluorobutanesulfonic acid (PFBS) as well as PFHxS, PFNA and PFDA have increased since “This indicates that the Swedish women have recently been exposed to increasing levels of PFHxS-related compounds from sources that are independent from PFOS exposure.” Glynne, Berger et al 2012, Perfluorinated Alkyl Acids in Blood Serum from Primiparous Women in Sweden: Serial Sampling during Pregnancy and Nursing, And Temporal Trends 1996–2010. https://pubs.acs.org/doi/abs/10.1021/es301168c	

			"PFHxS was only detected in Oslo, a potential indication for emissions as a PFOS substitute" Environmental pollutants in the terrestrial and urban environment, On behalf of the Norwegian Environment Agency, the Norwegian Institute for Air Research (NILU) in collaboration with Norwegian Institute for Nature Research (NINA) http://www.miljodirektoratet.no/Documents/publikasjoner/M354/M354.pdf	
IPEN/ACAT	5	12	Propose to emphasis the use of PFHxS used as an alternative to PFOS See e.g. uses in China of PFHxS as alternative to PFOS for Surfactants for AFFF Fluorocarbon surfactants for other applications Water proofing agent Textile finishing agents https://www.google.com/url?q=http://www.basel.int/Implementation/POPsWastes/TechnicalGuidelinesarchives/tabid/2381/ctl/Download/mid/13358/Default.aspx%3Fid%3D13%26ObjID%3D11613&sa=U&ved=0ahUKEwjXrpzd_6HaAhWJgVQKHd4vBFIQFggiMAQ&usg=AOvVaw0vkknNGSDY3fcyq9lzisxe "PFOS is being replaced by alternatives, for example fluorotelomer derivatives based on mainly 6:2 FTS for fire-fighting (Seow, 2013) and smaller PFAS such as PFHxS and PFBS for their stain repelling properties Environmental fate and effects of poly- and perfluoroalkyl substances (PFAS)" ©Concawe Brussels June 2016 https://www.concawe.eu/wp-content/uploads/2016/06/Rpt_16-8.pdf Appendix 3, Tab 6 of PFOS Alternatives lists PFHxS as an alternative to PFOS for Carpets, leather and apparel, textiles and upholstery Technical paper on the identification and assessment of alternatives to the use of	Introduction has been shortened but text has been added in 2.1.2

			perfluorooctane sulfonic acid, its salts, perfluorooctane sulfonyl fluoride and their related chemicals in open applications. UNEP/POPS/POPRC.12/INF/15/Rev.1	
IPEN/ACAT	5	12	Propose to emphasis the use of PFHxS used as an alternative to PFOS See e.g. " In recent years, surfactants in foam-based fire-fighting agents, used to extinguish flammable liquids or gases, shifted from long-chain PFASs (mainly C8-based) to short-chain PFASs (mainly C6-based)" Brendel et al. Environ Sci Eur (2018) 30:9 https://doi.org/10.1186/s12302-018-0134-4 https://enveurope.springeropen.com/track/pdf/10.1186/s12302-018-0134-4 Over the last several years, manufacturers of aqueous film forming foams AFFF have been replacing long-chain fluorosurfactants based on perfluorooctanesulfonate (PFOS) derivatives/precursors or 8:2 FTOH (precursor of PFOA) with shorter-chain fluorosurfactants based on perfluorobutane sulfonate (PFBS) and perfluorohexanesulfonic acid (PFHxS) derivatives/precursors or derivatives of 6:2 FTOH, which is a precursor of PFHxA." https://www2.mst.dk/Udgiv/publications/2015/05/978-87-93352-15-5.pdf	Introduction has been shortened but text has been added in 2.1.2
IPEN/ACAT	26	109	applications, often as a replacement for PFOS. It is also	Text has been edited
Russia		Section 1.1	Section 1.1 Chemical Identity In paragraph 16 of the draft risk profile, it is indicated that the data on the experimentally determined physicochemical properties of PFHxS are limited, and several studies reported some empirical and estimated physicochemical properties of PFHxS and related compounds, although there are differences among these data. Table 2 of the draft risk profile shows selected simulated and experimentally determined physicochemical properties of PFHxS. Thus, the information on physicochemical properties of PFHxS presented in the draft risk profile requires clarification to avoid discrepancies among the data from different authors. At the same time, simulated and calculated physicochemical	For PFASs in general it is very difficult to experimentally measure some of the physicochemical properties. The text has been edited and references added. See new text.

			properties listed in Table 2 require scientific confirmation	
Russia		Section 2.1.1.	Section 2.1.1 Production, trade, and stockpiles Paragraph 25 of the draft risk profile indicates that information on the production of PFHxS, its salts, and related substances in the public domain is scarce and mostly qualitative rather than quantitative. Paragraph 26 of the draft risk profile shows that two OECD reviews reported on the production of some PFHxS, its salts, and related compounds, but there is no information about the respective production volumes and locations. Thus, the draft risk profile should be supplemented with reliable information about the quantities and locations of production of PFHxS, its salts, and compounds related to PFHxS	It is already stated in the text that there was no information. "Similarly, the subsequent two OECD surveys reported the production of some PFHxS, its salts and PFHxS-related compounds, but with no information on their respective production volumes and locations (OECD, 2006, 2010)". For further information on the current knowledge on the production and use - see comments to The Netherlands question.
Russia		Section 2.1.3.	Section 2.1.3 Releases into the environment In paragraph 37 of the draft risk profile, it is indicated that to date, only limited research has been conducted to specifically study the releases of PFHxS, its salts, and PFHxS-related compounds into the environment, thus resulting in a lack of quantitative information on such releases. The presence of PFHxS and related compounds in the environment is the result of anthropogenic production, use, and disposal because they are not naturally occurring substances. Unintentionally produced PFHxS, its salts, and PFHxS-related compounds that are byproducts contained in perfluorooctanesulfonic acid (PFOS), its salts, and PFOS-related compounds are likely to have the same release pathways as the respective PFOS, its salts, and PFOS-related compounds. Thus, the lack of research on the conditions of formation and on quantification of releases of PFHxS, its salts, and related compounds into the environment and the lack of reliable data on possible pathways of the release and transformation of PFHxS, its salts, and related compounds in the environment give reasons to talk about the need for additional research in this area.	As stated in section 2.1.1. " It is likely that the ratios of PHxSF yields to POSF yields in the production of POSF are between 4% (Gramstad and Haszeldine, 1957) and 14.2% (reported by a Chinese manufacturer; Ren, 2016). This is supported by measured ratios of PFHxS to PFOS in commercial PFOS product, namely 3.5%–9.8% in 3M's FC-95 (3M, 2015) and 11.2%–14.2% in three products from China (Jiang et al., 2015)." Regarding the comment on quantitative information on release we have tried to collect this information from manufacturers and appliers of PFHxS, its salts, and PFHxS-related compounds during the analysis of the market research reports and the survey among stakeholders (presented in Norwegian Environment Agency Report M-961/2018). We did contact a number of producers, users and companies that offer these compounds for sale, with very few results. The market research report provided some information of varying quality but the stakeholder survey gave basically no results. The contacted companies either refused to answer, hang up when approached by phone (native speaking) or told us they would get back to us

				(which they did not do). A number of companies also replied that they did not sell/produce/use these substances even in the cases where they offer them for sale on their web page. Miteni (producer) in Italy has also been contacted both in English and Italian but they have no willingness to answer any questions. Hence, there is no clear picture of the applications of PFHxS and the amounts used and released to the environment. It is up to the companies to manufacture, use and apply PFHxS, its salts, and PFHxS-related compounds to come forward with this information. We do not think that the industries lack of willingness to provide information should benefit them in any way and we hope that at some point the industry or their branch organisations understand that they will benefit from releasing information.
Russia		Section 2.2.	Section 2.2 Environmental fate 2.2.1 Persistence Paragraph 40 of the draft risk profile contains the words "Experimental data on the persistence of PFHxS persistence are very scarce". Meanwhile, paragraph 42 of the draft risk profile says that according to the approach based on literature review, conclusions about the persistence of other perfluorinated alkyl sulfonates (hereafter: PFASs) such as PFOS and perfluorobutane acid (PFBS) may be valid for PFHxS as well. Accordingly, PFHxS is not expected to undergo hydrolysis or photolysis and biodegradation, and just as other PFASs, may turn out to be poorly removed by WWTPs (wastewater [sewage] treatment plants). Meanwhile, there are no other degradation studies on PFHxS. Nevertheless, in accordance with paragraph "b" of Annex D to the Convention on the criterion of persistence related to chemical compounds, the draft risk profile should provide information about the half-life of a substance in the various environmental objects, not just assumptions and comparisons with analogues.	The section on Persistence has been significantly changed. Information on the use of read-across has been added in the Introduction and in the Persistent sections – please see new text.

			Thus, for evaluation of the persistence of PFHxS and for implementation of paragraph "b" of Annex D of the Convention on the criterion of persistence related to chemical compounds, further studies are required.	
Russia		Section 2.2.2.	Section 2.2.2 PFHxS precursors and degradation According to paragraph 43 of the draft risk profile, a theoretical assessment of abiotic degradation pathways to PFHxS has been performed, and according to the results of this study, the substances containing the [C6F13S02] moiety may undergo abiotic degradation causing a release of PFHxS and C6 perfluoroalkyl carboxylic acids (hereafter: PFCAs). From PFOS degradation studies, one may expect that major products of abiotic degradation are likely to be PFCAs rather than PFHxS (10:1), whereas the main products of biotic degradation will be PFHxS almost exclusively. Thus, the observed theoretical discrepancies require experimental validation via additional research. Paragraph 44 of the draft risk profile indicates that analytical methods for identifying and quantifying PFHxS-related compounds are very limited at present. Accordingly, the lack of adequate methods for identifying and quantifying PFHxS-related compounds casts doubt on the results of the detection of PFHxS precursors presented in paragraphs 44, 45, and 46."	The section on PFHxS precursors and degradation on has been significantly changed. Information on read-across has been added – please see new text. It is right that you might expect a 10:1 ratio between PFCA and PFHxS which mean that you will still have 10% PFHxS as a degradation product. The theoretical assessment is supported by experimental studies of C4 and C8 and a read-across approach has been used to support the conclusion on PFHxS-precursor degradation. Furthermore, a number of the PFHxS-precursors have been detected in the environment.
Russia		Section 2.2.3.	Section 2.2.3 Bioaccumulation and toxicokinetics Paragraph 47 of the draft risk profile shows that log Kow could not be measured experimentally because of surfactant properties of PFHxS, given that this substance is expected to form multiple layers in an octanol–water mixture. Therefore, log Kow, as a bioaccumulation potential descriptor, is not suitable for PFHxS and related substances. Furthermore, the reported bioconcentration factors (BCF) and bioaccumulation factors (BAF) for PFHxS do not exceed the numerical criterion of 5000, indicating a low bioaccumulation potential in aquatic organisms.	The use of logKow and BFCs for PFAS in general has been discussed a number of times at POPRC and extensively in the literature and it is concluded that these numeric parameters are not suitable criteria for PFAS. The convention contains additional criteria for bioaccumulation - please see Annex D for further explanations of the additional B-criteria.

			Thus, on the basis of the numerical criterion of BCF and BAF (less than 5000), PFHxS cannot be classified as a persistent organic pollutant in accordance with Annex D of the Convention. In addition, the above statements about log Kow are based on assumptions and require scientifically valid evidence.	
Russia		Section 2.2.4	Section 2.2.4 The potential for long-range transfer in the environment Paragraph 54 of the draft risk profile indicates that the pathway governing the long-range environmental transport of individual PFASs in the environment has yet to be determined definitively. According to paragraph 56 of the draft risk profile, the higher frequency and levels of PFAS detected in the ocean waters compared to what has been detected in the air, as well as the relatively high solubility in water, indicate that the major pathway for the transfer of PFAS to remote areas involves water flows. Several studies have shown that PFAS precursors (e.g., PFBS, PFOS, and most likely PFHxS) are transferred via air and degraded. The potential for long-distance transfer of PFHxS in the environment through air is further supported by the detection of PFHxS in a lichen from the Atlantic peninsula. Lichens accumulate pollutants from the air and are bioindicators of air pollution. Because the capacity of a substance for long-range environmental transport is still one of the defining criteria for classification as a persistent organic pollutant, more research is needed to obtain scientific evidence of cross-border transport of PFHxS, its salts, and related substances and to identify dominant migration pathways from the possible sources of contamination.	There is a substantial amount of data from the Arctic region on long-range transport of PFHxS. Using results of detection of PFOS- and PFBS-related compounds it is anticipated that PFHxS-related are transported over long distances. Furthermore, this argument is strengthened by the detection of increasing amount of PFHxS during snow melt (Codling et al., 2014; Meyer et al., 2011) and detection of PFHxS in rain water (Eschauzier et al 2010).
Russia		Section 2.3	Section 2.3 Exposure 2.3.1 Environmental levels and trends Paragraph 62 of the draft risk profile indicates that several studies have presented temporal trends for levels of PFHxS in different species and matrices. Nevertheless, there are some discrepancies among these data, and the trends are increasing, decreasing, or show no consistent change. As mentioned above, the trend of PFHxS in polar bears in the European Arctic (Svalbard, Norway) is	There are discrepancies in the trend data. Recent studies show increasing levels in Arctic matrixes. Hence, we agree that the temporal trend in each case is most likely dependent of emission sources, food choices (terrestrial, marine) and location (urban versus rural) among other factors.

			increasing, while there is no such trend in Arctic foxes. Hence, the temporal trend in each case is most likely dependent on emission sources, food choices (terrestrial, marine), and location (urban versus rural) among other factors. Consequently, more research is needed to confirm the significant correlation of the levels of PFHxS in different species and matrices with the identified sources of PFHxS influx into the environmental objects, and this research will eliminate the existing discrepancies in the monitoring data.	
Russia		Section 2.4	Section 2.4 Hazard assessment for endpoints 2.4.1 Toxicity to aquatic organisms According to paragraph 76 of the draft risk profile, it is also known from other laboratory studies that PFHxS levels are moderately high and slightly chronically toxic in aquatic organisms, and in the few available studies on PFBS, its lower toxicity is shown. We believe that it is necessary to clarify the definition of "slightly chronically toxic" and the quantitative criteria for such toxicity.	Text has been rewritten.
Russia		Section 2.4.3	Section 2.4.3 Human toxicity In paragraph 87 of the draft risk profile, the results of studies about the effects of PFHxS on the total cholesterol level (hereinafter: TC) reveal significant discrepancies: both negative and positive links between PFHxS and TC have been found. A detailed analysis (of the results of epidemiological studies on the effects of PFHxS, its salts, and PFHxS-related compounds on the functional state of the thyroid gland and of research on the possible connection with neurotoxic and neurotrophic effects with immunotoxic actions, reproductive disorders, and the prevalence of osteoporosis, cited in paragraphs 88, 89, 90, 91, and 92) suggests that additional experimental and epidemiological studies are needed, where it is necessary to determine possible dose dependence of aberrations in the human body under the influence of PFHxS,	Comment noted. Some of these effects are supported by observations presented in Section 2.4.2.
China		13 and 34	About the draft risk profile on PFHxS, its salts and PFHxS-related compounds, in paragraph 13 and paragraph 35, the	No changes made. The original document (Huang et al 2010) has been translated by a native Chinese and

			production of surface treatment products containing PFHxSF- or perfluorobutansulfonyl fluoride (PFBSF)-derivatives was wrongly printed and cited in the references (1 k/a in the original document), which should be 1 t/a instead of 1000 t/a. Currently the production is under investigation. Considering the data was neither up to date nor accurate, the relevant descriptions are suggested to be deleted from the draft	referenced correctly. We are also stating in the risk profile (para 35 in second draft) that "no recent update of this estimate is currently available". Hence, while awaiting new data we will keep the text as it is.
China	8	27	The Chinese enterprises mentioned in the last sentence of paragraph 27 in page 8 are mostly commercial companies. The reference could prove that these companies might sell the products, rather than that they produce. So it is suggested that relevant content be deleted from the draft risk profile in question as well as from the reference.	No changes made. There is no information that confirms that these companies do not produce PFHxS, its salts and PFHxS-related compounds. Hence, unless information can be provided regarding where they get their supply of PFHxS and PFHxS-related compounds from the text will be kept as it is.
China	16	61	The last sentence of paragraph 61 in page 16 - "It has also been reported that PFSA emissions from China have increased since 2003 (Wang et al., 2017)."is inconsistent with the content of the reference, which it is suggested to delete.	Text has been deleted.
China	25	110	Due to the fact that the third sentence of paragraph 110 in page 25 lacks evidence, it is suggested the sentence - "One European manufacturer and a number of producers located in China have been identified, however, quantitative production data are not publically available."- be deleted	No changes made. See answer above (paragraph 27 on page 8)